The Model

0.1 The proposal

Let us consider the following mathematical model:

$$\frac{dx(t)}{dt} = f(x(t)) + \frac{a}{K + y(t)} \tag{1}$$

$$\epsilon \frac{dy(t)}{dt} = -y(t) + \frac{x(t)}{f + gu(t)} \tag{2}$$

with $\epsilon << 1$. This ensures time scale separation and from now it can be considered that (from the second equation):

$$y(t) = \frac{x(t)}{f + gu(t)}, \tag{3}$$

i.e. equation (3) corresponds to a readout of the system.

Remark 1 *Equations (1)-(2) describe the continuous non-linear time-invariant behavior of two biochemical species, x and y. The first equation says that the rate of change of x involves a positive feedback loop (*i.e. *$f(x)$ and a inhibition action due to y). The second equation says that the rate of change of y is affected by degradation (*i.e. $-y$) and a inhibition action and a negative feedback loop involving x and an input u, which drives the behavior of the system.

The assumption considered above allows us to study the stability behavior of the whole system just taking into account the first equation, which can be rewritten as follows:

$$\frac{dx(t)}{dt} = f(x(t)) + S, \tag{4}$$

where:

$$S := \frac{a}{K + \frac{x(t)}{f + gu(t)}}. \tag{5}$$

The time scale separation assumption would only provide bi-stability if $f(x(t))$ is a cubic function. We propose for this the following:

$$f(x(t)) = \frac{V_{max} x^n(t)}{K_m^n + x^n(t)} - \lambda x(t), \tag{6}$$

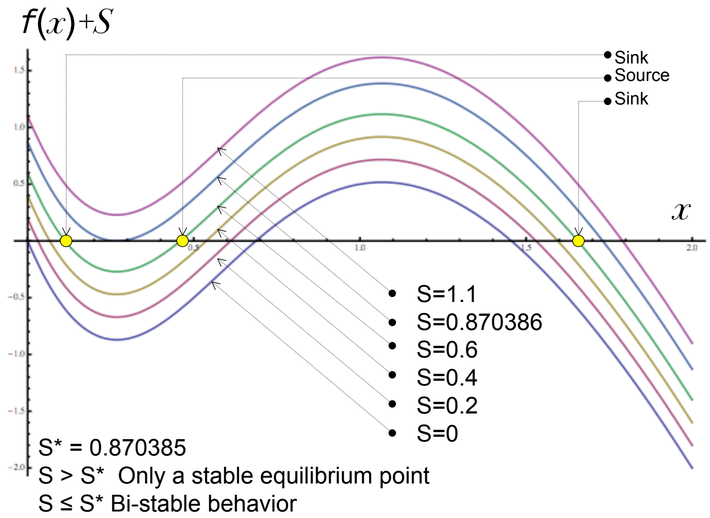

Figure 1: Stability analysis in terms of the value of S.

with $n \geq 2$ (co-operativity assumption). From now we shall consider n to be equal to 2 and we shall take the following values for the parameters involved in $f(x(t))$:

$$V_{max} = 15 \quad K_m = 1 \quad \lambda = 7$$

Remark **2** *Equation 6 assumes that the expression of x is activated by itself and that there is a degradation action on the rate of change of this species.*

0.2 Stability analysis

In order to see the evolution of the equilibrium points of the first equation (in terms of the value of S) we play with the value of S (by the moment we shall not consider that S in fact is dependent of both $x(t)$ and $y(t)$).

As far as the parameters of the inhibition actions on (1) and (2) equation are concerned, we shall take the following values:

$$a = 1 \quad K = 1 \quad f = 0.01 \quad g = 1$$

When considering the fixed point of the the equation (4), *i.e.*:

$$f(x(t)) + S = \frac{15x^2(t)}{1 + x^2(t)} - 7x(t) + S,$$

we have that:

- for $S > S^* = 0.870385$ the system only has a equilibrium point, which is stable (*i.e. a sink*).
- for $S \leq S^*$ the system can display bi-stable behavior.

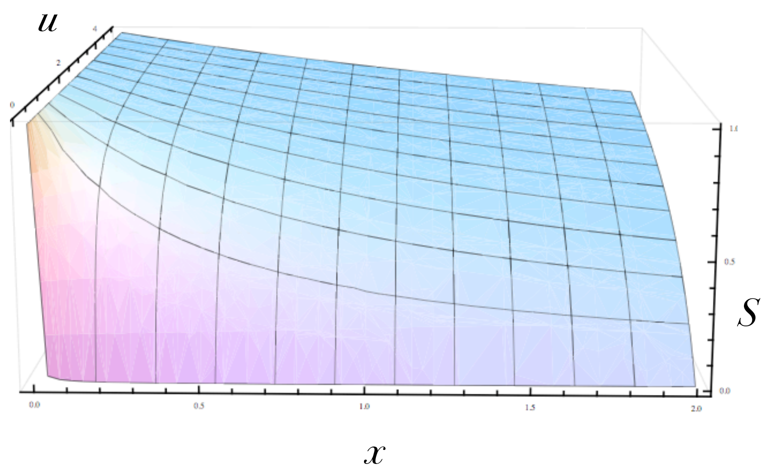

Figure 2: Interplay between x, S, and u.

We have the following situation:

Equilibrium point	$S = 0$	$S = 0.870385$
x_1	0	0.266163
x_2	0.686774	0.269992
x_3	1.45608	1.7311

For $S^* < S = 0.870386$ the system has as its only (stable) equilibrium point $x = 1.73111$ (for $S > S^*$, x grows up as far as S grows up).

Remark **3** *From the previous analysis we conclude that the bi-stable behavior of the system will only be displayed when $S \in [0, 0.870385]$. Moreover, we will be only interested in what happens with the system when its time evolution is constrained to $\alpha =: 0.01 \leq x \leq 1.74 =: \beta$.*

Remark **4** *The bifurcation analysis allows us to compute some sufficient conditions on the parameters a, K, f, and g, in order to guarantee bi-stability of the original system (1)-(2). The conditions involve alpha and β.*

As far as the initial conditions are concerned, we have that only $x(0)$ will affect the behavior (because of time scale separation). The interplay between the values of x, S, and u, is shown in Figure 2. For given values of x and u, the vertical position shows the resulting value of S. If the values for x and u are such that $S \leq S^*$, the system will be evolving in the bi-stable mode.

0.3 Computer simulations

In what follows we describe the computer-based simulation setup, as well as the results obtained from the simulations.

Active negative feedback See Figure 3. The red circles correspond to steady states resulting when the system evolves around the first stable region. Every single steady state is obtained when applying a step function which is first equal to zero for the first 10 seconds and that changes later to a constant input, remaining in that value until the steady state is attained. For the black circles, they correspond to the behavior of the system in the second stable region, and they result after the transition from the first stable region, which happens when the input is greater than a given threshold (here the value is 1.95). Once the transition makes the system to change from the first stable region to the second one, it is applied the same procedure which gives rise to the first case (red circles). As can be seen (black circles), the response of the system is now different, evidencing the existence of the memory based mechanism associated to bi-estability.

Non-active negative feedback See Figure 4. In this case we consider the first equation to be $\frac{dx(t)}{dt} = f(x(t)) + \frac{a}{K}$ (the negative feedback loop is now inactive, *i.e.* $S = a/K = 1.0 > S^* = 0.870385$, which implies that the steady state state of the system will be in the second stable region). The black circles correspond to the case when the feedback is active, whereas the blue circles correspond to the case when the negative feedback loop is not working. As can be seen the system evolves in the second region of stability, and for each u the resulting values of the output (for both the the active feedback case and the non active feedback case) are close.

Remark **5** *For all the simulations considered above we use as initial condition the vector* $(x(0) = 0.1, y(0) = 0.1)$.

Just to conclude here, Figure 5 shows the transition from the first stable region to the second one when the negative feedback is non active, for the case when the input $u(t)$ is a step (for the first 10 seconds the value is 0 and for then the constant value is equal to 0.9).

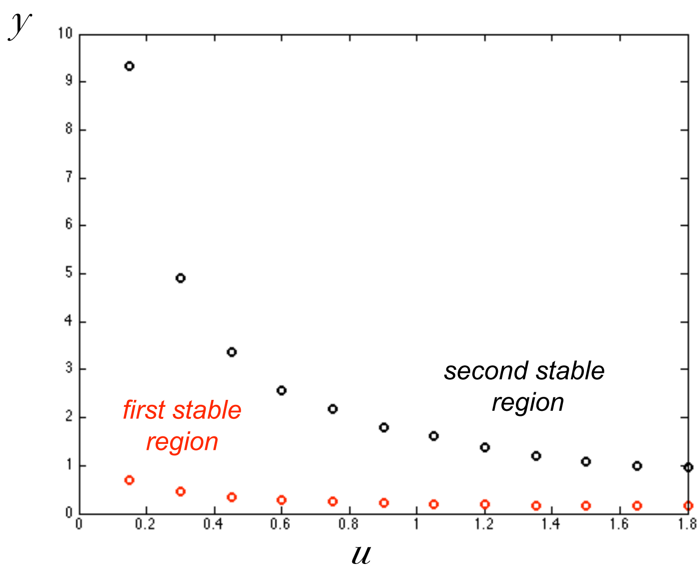

Figure 3: Behavior of the model when the negative feedback loop is active.

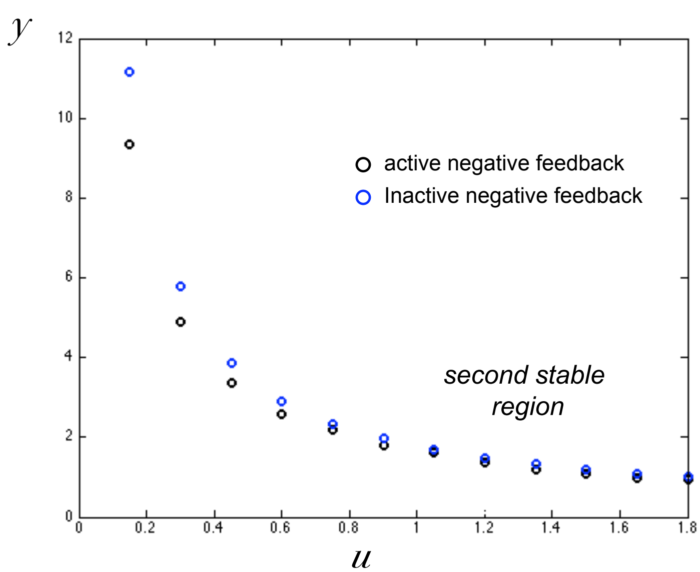

Figure 4: Behavior of the model when the negative feedback loop is not working.

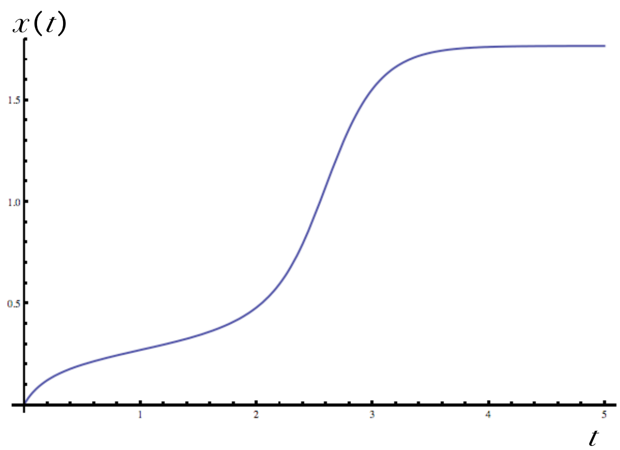

Figure 5: Transition from the first stable region to the second one, when the negative feedback loop is not working.